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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/303,232	04/30/1999	MARTIN ADAMCZEWSKI	MO-5176/LEA3	8055

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/303,232	Adamczewski
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 21, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-7, 10, 22-31, and 35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-7, 10, 22-31, and 35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Apr 30, 1999* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 31 on 11/21/02.

Claims 1, 34, and 36 were canceled as requested.

Claims 2-7, 10, 22-31 and 35 remain pending and under consideration in this Office Action.

The previously indicated allowability of claim 35 is withdrawn in favor of the following new grounds of rejection which render this Office Action NON-FINAL.

Claim Objections Withdrawn

The objection to claim 10 is withdrawn in view of Applicants amendment.

Rejections Withdrawn

The rejection of claim 10 are under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicants amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

1. Claims 2-7, 10, 22-31 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in Paper No. 25.

2. The claims are drawn to nucleic acids that encode a complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells. The nucleic acids must comprise either nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , or nucleotides 95-1597 of SEQ ID NO:5; complements of one of these sequences; or sequences encoding the same polypeptide as one of these sequences. However, the claims do not require that the recited complete or partial insect acetylcholine receptor subunit must be encoded by nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , or nucleotides 95-1597 of SEQ ID NO:5. The claims require only that these sequences, or their complements or degenerative equivalents, must be present in the nucleic acid. For this reason, the claims embrace nucleic acids encoding any complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells, wherein the nucleic acid also encodes nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , or nucleotides 95-1597 of SEQ ID NO:5. In other words, the claims embrace nucleic acids

comprising any one of the three disclosed sequences combined with a sequence encoding any complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells.

This genus includes nucleic acids which hybridize to specific subsequences from SEQ ID NOS: 1, 3, or 5, such as those specifically recited in claims 22 and 23. Such sequences lack adequate written description for the reasons of record in Paper No. 29, reiterated below.

The claimed genus encompasses nucleic acids which hybridize to specific subsequences from SEQ ID NOS: 1, 3, or 5 under certain conditions. The subsequences correspond to the open reading frames encoding the homooligomeric receptors, and are bases 372-2681 of SEQ ID NO:1, bases 335-1822 of SEQ ID NO:3 , and bases 95-1597 of SEQ ID NO:5. A sequence search performed by the PTO indicates that these subsequences of SEQ ID NOS: 1, 3, and 5 display substantial variability with respect to each other. The subsequence of SEQ ID NO:1 is about 22% identical to the subsequence of SEQ ID NO:3 , and about 27% identical to that of SEQ ID NO: 5, whereas the subsequences of SEQ ID NOS: 3 and 5 are about 38% identical to each other. See sequence alignments attached to Paper No. 25.

The following analysis is based on the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage on the treatment of genus claims is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation

between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The first question for consideration is whether the reduction to practice of three species of functional homooligomeric insect acetylcholine receptor subunit nucleic acids is sufficient to satisfy the description requirement. The three described species display substantial variability as noted above, indicating that there is substantial variation in the genus. In fact, a search by the PTO found that nucleic acids encoding mammalian homooligomeric alpha 7 acetylcholine receptors showed a similar level of identity to the disclosed insect sequences as the insect sequences did to each other. For example, a nucleic acid encoding a mouse alpha 7 acetylcholine receptor subunit is about 28% identical to bases 335-1822 of SEQ ID NO:3 , whereas bases 372-2681 of SEQ ID NO:1 are only 22% identical to this subsequence of SEQ ID NO:3 . Further, a nucleic acid encoding a human alpha 7 acetylcholine receptor subunit is about 25% identical to bases 95-1597 of SEQ ID NO:5, compared to the 27% identity between the subsequences of SEQ ID NOS: 1 and 5. See sequence alignments attached to Paper No. 25. Because the degree in variability between the claimed insect sequences is large, and is similar to the variability between insect sequences and mammalian sequences, the reduction to practice of SEQ ID NOS: 1, 3, and 5 is insufficient to adequately describe the genus of functional insect homooligomeric acetylcholine receptors.

Next it must be determined if Applicant has disclosed any relevant identifying characteristics of the genus. Although SEQ ID NOS:1, 3, and 5 all encode polypeptides sharing a common activity, neither the specification nor the prior art teaches any specific correlation

between any physical structure of the nucleic acids and the ability of the encoded products to form complete or partial insect homooligomeric acetylcholine receptors. Thus it is unknown what common structural features allow a nucleic acid to encode a protein with the function of an insect homooligomeric acetylcholine receptor, although it is apparent that substantial structural variation may occur within the broad genus of nucleic acids encoding these receptors as indicated by the low degree of sequence identity between SEQ ID NOS: 1, 3, and 5. One might argue that the encoded proteins show a reasonable degree of amino acid sequence similarity, however in the absence of any disclosure of what particular sequences are required to fulfill the critical requirement of encoding complete or partial functional homooligomeric insect acetylcholine receptors, there can be no disclosure of any structure/function correlation which provides an adequate written description of the claimed genus.

In addition the claimed genus embraces nucleic acids encoding any complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells, without limitation as to the sequence of the portion of the nucleic acid encoding the subunit. An adequate written description of a DNA requires more than a mere definition of a biological property, i.e. any complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells, because disclosure of no more than that, is simply a wish to know the identity of any polynucleotide with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that

material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the polynucleotide has been isolated. Thus, claiming all polynucleotides that achieve a result (i.e. encoding any complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells) without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

This rejection may be overcome by requiring that the insect acetylcholine receptor subunit encoded by the nucleic acid must be encoded by nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , or nucleotides 95-1597 of SEQ ID NO:5.

It is suggested that the phrase "wherein nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , and nucleotides 95-1597 of SEQ ID NO:5 encode an acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in a host cell" should be substituted for the last three lines of instant claim 35.

It is further suggested that claims 22 and 23 should be canceled because these claims would still embrace inadequately described species, even after the suggested amendment to claim 35.

Enablement

3. Claims 2-7, 10, 22-31 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids which encode the polypeptides of SEQ ID NOS: 2, 4 and 6, does not reasonably provide enablement for a nucleic acids encoding a functional insect homooligomeric acetylcholine receptor as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

4. *Nature of the invention and Breadth of the claims*

The claims are drawn to nucleic acids that encode a complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells. The nucleic acids must comprise either nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , or nucleotides 95-1597 of SEQ ID NO:5; complements of these sequences; or degenerative equivalents of these sequences. However, the claims do not require that the complete or partial insect acetylcholine receptor subunit must be encoded by nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , or nucleotides 95-1597 of SEQ ID NO:5. The claims require only that these

sequences must be present in the nucleic acid. For this reason, the claims embrace nucleic acids encoding any complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells, wherein the nucleic acid also encodes nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , or nucleotides 95-1597 of SEQ ID NO:5. That is, the claims encompass any nucleic acids that encodes any complete or partial insect acetylcholine receptor subunit having the ability to form homooligomeric acetylcholine receptors when expressed in host cells, as long as that nucleic acid also encodes nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , or nucleotides 95-1597 of SEQ ID NO:5.

5. *State of the art, Predictability of the art, Guidance and Examples in the specification, Level of skill in the art, and Amount of experimentation required*

The specification and the prior art teach that the sequences of several vertebrate homooligomeric acetylcholine receptors were available at the time of filing. However, the specification fails to teach which amino acids are required for function, and which positions can tolerate substitutions. While it is known that many amino acid substitutions are generally possible in any given protein, certain positions in a polypeptide sequence are critical to the protein's structure/function relationship, such as various sites or regions where the biological activity resides or regions directly involved in binding, stability or catalysis, or which provide the correct three-dimensional spatial orientation for biologically active binding sites, or which represent other properties or characteristics or properties of the protein. These or other regions may also be

critical determinants of activity. These regions can tolerate only relatively conservative substitutions, or no substitutions. See Bowie et al (1990). The prior art teaches that the effects of amino acid substitutions and deletions on protein function were highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". Applicant has provided little or no guidance to enable one of skill in the art to determine, without undue experimentation, the positions in the claimed nucleic acids which are tolerant to change, and the nature and extent to of changes that can be made in these positions in order to retain function as required by the claims. Even if critical residues were identified in the specification, which they are not, the mere identification of these residues as critical would not be sufficient, as the skilled artisan would immediately recognize that critical sites must assume the proper three-dimensional configuration to be active, and that conformation is dependent on surrounding residues as well. Thus alterations in sequences which are not apparently part of a catalytic center or binding site can destroy activity by altering the overall conformation of a protein.. One might argue that it would not be undue experimentation to express and assay

polypeptides individually using the assays taught in the specification, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. The specification fails to provide any theoretical framework which can be used to accurately predict which amino acid substitutions will eliminate receptor function, and which will be tolerated as required by the claims. In the absence of such guidance, even those of the highest skill in the biotechnological art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

This rejection may be overcome by adopting the suggestions at the end of the preceding written description rejection.

Response to Arguments

6. Applicant's arguments filed 11/21/02 have been fully considered but they are not persuasive. Applicant asserts at pages 5 and 6 of the response that amendments to the claims overcome the basis of the rejections. This is unpersuasive for the reasons set forth in the rejections above. Briefly, the claims are written in an open format that does not require that the

sequence encoding an acetylcholine receptor subunit must also be a sequence encoding the polypeptide encoded by nucleotides 372-2681 of SEQ ID NO:1, nucleotides 335-1822 of SEQ ID NO:3 , or nucleotides 95-1597 of SEQ ID NO:5. Instead, there is no limitation on the nature of the sequence that actually encodes the acetylcholine receptor subunit, except that it must be physically linked to one of the three sequences listed above, its complement, or its degenerative equivalent. This necessitates the preceding rejections.

Summary

Claims 2-7, 10, 22-31 and 35 are rejected under 35 U.S.C. 112, first paragraph as lacking adequate written description and enablement.

Conclusion

No claim is allowed

All claims are free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JEFFREY SIEW
PRIMARY EXAMINER
1/26/03